

CHANGES IN BLOOD SERUM CALCIUM FOLLOWING THE ADMINISTRATION OF PARATHYROID EXTRACT

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EDITORIAL NOTE—*The important research by Doctors Sherrill and Copp of the Scripps Metabolic Clinic is so timely that the date of publication is advanced. The work was presented at the annual dinner of the San Diego County Medical Society December 9, 1925.*

THE recent announcement by Collip^{1 2 3} of the extraction of a parathyroid hormone, which prevents parathyroid tetany and regulates the level of blood calcium, adds greatly to our knowledge of the glands of internal secretion. From experimental data thus far obtained, the extract is as specific in parathyroid insufficiency as insulin has proved to be in pancreatic insufficiency. Previous to the work of Collip, numerous reports of beneficial effects following the use of parathyroid extract have occurred in the literature, but with the exception of the work of Hanson⁴ the majority are rather unconvincing. There is little doubt but that Hanson isolated the hormone and reported the method of preparation previous to the publications of Collip. However, not until recently⁵ did he demonstrate the calcium regulating effect of the extract.

The discovery of the parathyroid glands belongs to Sandstrom (1880), although he did not describe the histological differences between the parathyroids and the thyroid. He believed that the small bodies which he noted were simply embryonic remnants of thyroid tissue. Gley, in 1891, rediscovered the parathyroids. He attributed death following thyroidectomy to the removal of the parathyroids, rather than to the removal of the thyroid tissue. As early as 1834 Raynard described early fatality coincident with the removal of the thyroid gland. Two Italian investigators, Vassle and Generali, in 1896 were the first to demonstrate the relation between the parathyroid glands and tetany.

Tetany may be described as a peculiar hyper-excitability of the nervous system (sensory, motor, autonomic). We are indebted to Clark and Kellie for the first clinical description of the condition. In 1815 they observed laryngospasm, rigidity of the extremities and tonic spasms in children, and other classical signs which occur in tetany. Similar clinical signs were described by Steinheim in 1831, and by Dance in 1831. Certain responses of the motor nerves are demonstrable by electrical and mechanical stimulation in tetany. Trousseau, in 1864, showed that the typical attitude of "obstetrical" hand occurred when a constricting band was applied about the upper arm to obstruct the flow of blood through the brachial artery. Chvostek showed that tapping the facial nerve caused contractions of the muscles of the corresponding side of the face, and Erb demonstrated increased electrical excitability of the motor nerves. The excitability can be determined, particularly with the kathodal opening contraction. In tetany contractions can be obtained upon application of currents below 5 milliamperes, whereas, in normal individuals much stronger currents are required.

The importance of mineral substances in tetany probably begins with the work of Sabbatini.⁶ In 1901 he called attention to the antagonistic relation between calcium and sodium salts. When calcium solutions were applied to the surface of the brain electrical excitability was reduced; while sodium solutions had the reverse effect. He mentioned the fact that calcium preparations might be of value in epilepsy. Loeb,⁷ in 1902, demonstrated that when solutions which precipitate calcium were injected into animals, thereby reducing the amount of available calcium present, marked hyper-excitability occurred. MacCallum and Voegtlin,⁸ in 1909, demonstrated the existing relation between calcium and hyper-excitability of nervous tissue. The withdrawal of calcium caused hyper-excitability, which was relieved when calcium was supplied. They formulated the theory that tetany was due to calcium deficiency, and showed that injections of calcium relieved tetany in parathyroidectomized dogs.

Howland and Marriott⁹ made determinations of serum calcium in normal children, rickets, idiopathic tetany, and convulsions. Sixteen normal children showed serum calcium values ranging from 9.2 to 11.2 milligrams per 100 cc., and twenty-one children with rickets from 8.8 to 10.7 milligrams per 100 cc., with a general average of 9.4. They showed rickets to be independent of tetany. Low calcium values were found in all cases of active tetany. In eighteen cases of idiopathic tetany the serum calcium ranged from 4.5 to 6.8, with a general average of 5.6. They did not find retention of inorganic phos-

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TABLE I

Thyroparathyroidectomized dog. Demonstrating fluctuations in blood serum calcium upon the withdrawal and the administration of parathyroid extract. This table also well illustrates the appearance of tetany co-incidental with low blood serum calcium.

Sept.	Hour	Blood Serum Calcium	Red Cell Volume Per Cent	NaCl	Para-thyroid Extract Units	REMARKS
15	3:00 p. m. 4:00 p. m.	10.8	38.1	626		Before operation. Thyroparathyroidectomy.
16	6:00 p. m.					Good condition. Ate bread.
17	10:00 a. m. 2:00 p. m. 2:15 p. m. 4:10 p. m. 4:15 p. m. 4:20 p. m. 6:00 p. m. 7:00 p. m. 7:30 p. m. 8:00 p. m.	6.2 6.7 6.8	 38.5 43.6	 626 601	 10 10 5	Mild muscular contractions. Muscular spasm and convulsive seizures. Convulsive seizures increasing. Convulsive seizures typical of severe tetany. Laryngospasm. Spasm of diaphragmatic muscles. Dyspnoea. Unable to stand. Unable to stand.
18	10:00 a. m. 2:50 p. m. 4:00 p. m.	7.2	41.6	614	 7 3	Breathing much quieter. Apparently sleeping. Tetany ceased. Breathing normal. Drinks water. No symptoms. No symptoms.
19	1:00 p. m.				5	Takes meat, bread, milk, but with difficulty in swallowing. Few twitches of abdominal muscles.
20	8:45 a. m. 10:30 a. m. 11:15 a. m. 2:00 p. m.	6.1	37	610	5	Eats normally. No tetany. Few fine tremors, abdominal muscles.
21	10:00 a. m.					Good condition. Fed meat and bone.
22	4:00 p. m. 4:30 p. m.				5	No tremors.
23	9:00 a. m.	6.2			5	A few slight tremors. Given bread and butter.
24	9:30 a. m.				4	Normal.
25	10:00 a. m. 10:00 a. m. 12:00 m.	5.5	33	593	5	Chattering of teeth. Twitching of muscles of head and neck when stimulated or excited.
26	9:00 a. m. 11:40 a. m. 8:30 p. m.	6.0			5	Tetany when cold or stimulated. Spastic gait. Tetany of right hind leg and jaw muscles.
27	9:00 a. m. 11:00 a. m. 7:00 p. m.				5 5 5	Few minor twitches. Tetany on exertion and when in cold draft. No symptoms.
28	9:00 a. m. 12:30 p. m. 10:30 p. m.	16.8			10 10 10	One slight shaking spell. Normal. Normal.
29	3:00 p. m. 2:30 p. m. 6:30 p. m. 7:30 p. m.	13.8			10 10 10 10	No evidence of tetany.
30	9:30 a. m. 10:30 a. m. 3:30 p. m. 7:30 p. m.	13.5	32.3	577	10 10 10 10	No tetany. No tetany.
Oct.						Refuses food.
1	1:00 a. m. 6:30 a. m. 12:00 m. 4:00 p. m.	17.6			10 10	Refuses food. Lacks usual vigor. Rather drowsy.
2	8:00 a. m. 7:00 p. m.	14.0				Dog is brighter. Eats and drinks fairly well. Lively, eats biscuits greedily.
3	8:30 a. m.	11.6				
4	9:00 a. m.	10.0				Dog is quite bright and eats well.
5	9:00 a. m.	10.0				Dog quite active.
6	9:00 a. m.	8.8				Acts normally.
7	9:00 a. m.	8.0				Shows no evidence of tetany.
8	9:00 a. m.	8.0				Eats and looks well.
9	9:00 a. m.	6.9				Normal.
10	9:00 a. m. 3:00 p. m. 3:30 p. m. 6:30 p. m.	5.2			5 5	Chattering of teeth. Lack of usual co-ordination of muscles. Fell down on attempting to jump. Signs of tetany reappearing. Spasm of right hind leg muscles. Jaw muscles fibrillary twitching.
11	9:30 a. m. 12:30 p. m. 7:05 p. m.	5.6			10	Muscle twitching worse. Will not eat. Has tetany in moderate degree. Clotting time of blood is five minutes. Particularly bad on awakening from several hours' nap. Muscular twitchings less marked. Ate large amount of food.

TABLE I—(Continued)

Oct.	Hour	Blood Serum Calcium	Red Cell Volume Per Cent	NaCl	Para- thyroid Extract Units	REMARKS
12	9:30 a. m.				5	Slight tremor. Good condition. Blood clotting time in capillary tube four to five minutes.
	10:00 a. m.	6.5				
13	9:45 a. m.	6.8			5	
14	9:45 a. m.	7.4			5	Dog appears normal.
15	9:00 a. m.	7.0				Slightly spastic in legs. Eats well and practically normal.
16	9:00 a. m.	6.2			5	More rigidity than yesterday.
17	9:00 a. m.	7.1				
18	9:00 a. m.	6.8				Temporal muscles twitching. Slight spastic gait.
19	10:00 a. m.	6.6				Chronic tetany.
20	9:00 a. m.	6.4				Slight spasticity of masseter muscles. Dog quite bright.
21	9:00 a. m.	6.0			10	Some spasticity of thigh muscles. Slight tremor of other muscles.
	2:00 p. m.					Tremors of muscles increased.
22	9:00 a. m.	5.8				Increased spasticity of all muscles.
	12:30 p. m.				10	Muscles of neck rigid. Swallows with difficulty.

phates associated with the low calcium values. Seven cases of convulsions not due to tetany, such as epilepsy, mental deficiency, etc., showed normal calcium of 9 to 11 milligrams per 100 cc.

Tetany occurs in several different types of clinical conditions, and can be produced by several measures. It is most commonly seen in association with rickets. The most classical signs are seen in idiopathic tetany, and in this condition the typically low serum calcium values are found. The administration of large amounts of sodium bicarbonate¹⁰ has been known to produce attacks of tetany. Grant and Goldman¹¹ produced tetany experimentally in normal individuals by means of forced respiration. In twenty-one experiments the subject breathed as deeply as possible at the rate of fourteen times per minute. Symptoms of tetany developed in all the experiments in from 15 to 60 minutes, and the common signs, carpopedal spasm, Erb's, Chvostek's, and Trousseau's signs could be elicited in most of the cases. In one experiment a typical tetanic convulsion occurred. They explained tetany on the basis of alkalosis, produced by washing out carbon dioxide from the alveoli, thereby reducing the carbon dioxide content of the blood, so tending to make the blood alkaline. They did not study the changes in blood calcium to any extent. A number of investigators, particularly Patton, Findlay, and Burns,¹² in 1916 attributed the occurrence of tetany to the toxic effect of guanidine and methylguanidin. Although symptoms of tetany may be produced by injections of the salts of guanidin and methylguanidin, the position of these investigators seems untenable in the light of present knowledge of the disease, especially so, considering the researches to the contrary by Greenwald.¹³

Of all the chemical components of the blood, calcium is probably the most constant. Its level is little affected by the usual factors which frequently affect the other constituents, such as disease, rest, exercise, food, and diet. The normal blood serum calcium ranges from 9.4 to 10.4 mg. per 100 cc. In only one condition, viz., tetany, is it affected to any extent. From a number of reliable sources it has been re-

ported to be as low as 4.4 mg. per 100 cc. in this disease. For the analysis of calcium we have used the micro method of Kramer and Tisdall¹⁴ without modification. The parathyroid hormone has a limited clinical application, because of the infrequent occurrence of diseases due to parathyroid insufficiency.

It is well known that the complete removal of all parathyroid tissue in dogs results in death within two to five days. Death is due to tetany, which begins gradually with hyper-excitability, muscular twitchings, fibrillary quivering, spasticity of the limbs, and finally leads to powerful clonic spasms and convulsions. In the late stages the laryngeal muscles and the muscles of deglutition are involved, and death finally results from respiratory failure. The administration of calcium salts affects, to some extent, the onset and progress. Serum calcium of dogs is distinctly higher than in the human. We consider 10 mg. to 12 mg. as normal.

The administration of calcium, either by mouth or intravenously, delays the onset of tetany in parathyroidectomized dogs, but they succumb after a short time. The injection of large amounts of fluid to promote diuresis also prevents the symptoms of tetany. Luckhardt and Rosenbloom¹⁵ were able to keep parathyroidectomized dogs alive for four to six weeks, simply by injecting large amounts of saline intravenously every day. They injected 33 cc. per kilo body weight at each injection. Tetany appeared when the injections were discontinued. They found that it was not necessary to administer calcium, provided diuresis was kept up by water alone.

The effective action of the recently discovered parathyroid extract can be specifically demonstrated in thyroparathyroidectomized dogs. It controls tetany promptly and we have been able to keep parathyroidectomized dogs alive for over two months. Collip has kept several alive for over five months. A unit of extract is considered as 1/100 of the amount of material which will produce an increase of 5 mg. in the serum calcium of a dog weighing 20 kilos within a period of fifteen hours. The rapid recovery from tetanic convulsions following the ad-

TABLE II

Hypercalcemia produced in a normal dog with overdoses of parathyroid extract.

Sept.	Hour	Calcium	Red Cell Volume Per Cent	NaCl	Para-thyroid Extract Units	REMARKS
26	9:00 a. m.	11.0	49	630	5	
	11:40 a. m.				5	
	8:30 p. m.	12.1			5	
27	11:00 a. m.	13.1			5	Normal.
28	9:00 a. m.	13.4			10	Normal.
	12:30 p. m.				10	
	6:00 p. m.				10	
	10:30 p. m.				10	
29	2:30 p. m.	19.2			10	
	3:00 p. m.				10	
	7:30 p. m.					No appetite. Stupid.
30	6:30 a. m.		47.1	532	10	No appetite.
	8:15 a. m.					Dog has vomited during night. Not nearly so lively.
	10:00 a. m.	19.0				
	10:30 a. m.				10	
	3:30 p. m.				10	
	4:15 p. m.					Dog attempts to vomit.
	7:00 p. m.					Vomits.
	7:30 p. m.				10	
Oct.						
1	1:00 a. m.				10	
	6:00 a. m.				10	
	12:00 m.	19.4	58			Vomited, stupid, not responsive.
	5:30 p. m.					Diarrhea. Hematemesis of 250 c.c. Refuses to eat. Very drowsy.
	9:00 p. m.					Restless, eyes dull, respiration quick and very audible. Keeps reclining position, whines.
2	8:00 a. m.					Died.

ministration of the extract is as remarkable as the recovery of a diabetic patient from deep coma following insulin therapy. We have seen many dogs in the severest forms of terminal convulsions restored to normal three to four hours after receiving the extract. The signs disappear in reverse order from that in which they appeared. We have not determined just how low the blood calcium may fall in terminal stages before reversible reaction is impossible. Reversible reaction is still possible with serum calcium values as low as 5.2 mg. per 100 cc.—the lowest figure we have yet encountered. It may be assumed that removal of the parathyroids lowers the threshold for calcium, and in this regard calcium is the only chemical element of the blood which is affected. We have not been able to detect changes in chloride, sugar, creatinine, urea or CO₂; other than alterations due to fluctuations in blood concentration.

We are including in this publication only two charts, selected from a large number of experiments. These illustrate practically all of the cardinal changes following the use of parathyroid extract.

The relative constancy of the level of serum calcium at which signs of tetany appear, in the same dog as well as in the species as a whole, is very striking. When the level falls to 7 mg. per 100 cc. signs usually appear, and there is a progressive increase in the condition as lower levels are reached. Several dogs in which we failed to remove all the parathyroid tissue developed mild chronic tetany, resulting in minor signs, such as slight spastic gait, muscular twitchings, associated with constantly low serum calcium of 7 to 8 mg. per 100 cc. The manner in which tetany appeared when the calcium fell below 7 mg., and disappeared when increased above this figure, by means of the extract, is shown very distinctly in Table I. It is possible for animals to

be entirely symptom-free, with low values of 5.5 to 6 mg., but this is the exception rather than the rule. Occasionally, we have observed clinical signs after the calcium had been elevated to 9 mg. or more, but this is also unusual. The blood calcium changes only very slowly after extract is given. Clinical improvement may occur before there is appreciable change in the serum calcium, as shown in Table I. The dog had severe convulsions when the blood calcium was 6.2 mg. per 100 cc., and the administration of 25 units of extract restored the dog to normal within a period of four hours, but during this time the blood calcium was elevated only .6 mg.

Small divided doses of extract administered at frequent intervals are more beneficial in elevating the calcium than a single dose. Pyramiding doses at intervals of a few hours raises the calcium rapidly. This is shown very distinctly in Table II. It will be seen that the repeated administration of 5 units of parathyroid extract on September 26 and 27 in Dog No. 2 brought about a rapid increase, while in Dog No. 1, 5 units of extract daily on October 12, 13, and 14 brought about very little change. The duration of elevation depends on a number of factors, such as body weight, height of blood calcium at the time of injection and upon the dose of extract administered. Relation of the size of the dose injected to the body weight is more important than in the administration of insulin. For instance, we have seen 20 units of parathyroid extract raise the blood calcium of a baby, weighing 17 kilos from 12 mg. per 100 cc. to 15.5 mg. per 100 cc. within a period of eight hours, whereas the injection of a similar dose to an individual weighing 75 kilos increased the serum calcium from 10 mg. per 100 cc. to only 10.2 mg. per 100 cc. in a similar length of time.

Collip¹ described a condition of hypercalcemia

TABLE III

Changes in blood serum calcium, coagulation time and red cell volume in various types of clinical conditions.

Serum Calcium		Coagulation Time		Red Cell Volume		Para-Thyroid Extract Units	Time Days	Diagnosis
Before	After	Before	After	Before	After			
9.8	10.9	5	4	36	32.6	60	4	Arthritis
9.3	10.1	3	4	29.2	31.7	60	4	Arthritis
9.6	10.7	7½	3½	29.7	.	45	8	Arthritis
9.4	12					60	3	Arthritis
9.4	11.2	4	3	42	37.5	120	7	Paralysis agitans
10.6	12.8	5½	3½			50	6	Paralysis agitans
9.6	11.6					120	3	Paralysis agitans
9.2	11.8	7½	5	40	40	35	4	Hemophilia
9.2	10.4					100	3	Hemophilia
8.2	10.2	12½	5	47	44	70	5	Hemophilia
10.4	15.4					212	33	Mental deficiency with convulsions
10.8								Mental deficiency with convulsions
10.1	11.6					100	10	Epilepsy
9.7	11.7	4	3	25.6		45	8	Gastric ulcer
9.1	10.8	2	2	44.2		50	8	Neurosis
7.7								Purpura haemorrhagica
9.7	Average for 50 patients.							
11.2	Average for 40 dogs.							

following overdosage of parathyroid extract. It is a very simple matter to produce hyper-calcemia by overdosage, and in our clinical work we have been very cautious in its use. Definite symptoms follow overdosage in dogs. The earliest and most frequent finding is stupor. The dog becomes listless and makes very little effort to move or to notice his surroundings. Anorexia soon develops. They cannot be encouraged to take either food or water. As the calcium is further increased, vomiting occurs and is very persistent. If water or food is administered by mouth during this period, vomiting promptly ensues. Later, hematemesis and bloody diarrhea occur. If the extract is discontinued as soon as vomiting occurs, the dogs recover, but we have found no beneficial therapeutic measures after hematemesis begins and the animals die within a few hours. We have been able to produce hyper-calcemia in parathyroidectomized dogs as easily as in normal dogs. When large amounts of extract are given to produce hyper-calcemia the blood calcium can be increased to as much as 19 mg. per 100 cc. It seems that a plateau is reached when such concentration is produced, and further injections of large amounts of extract have not increased the blood calcium beyond this point. This is shown very distinctly in a normal dog (Table II) when repeated doses of the preparation were administered.

Changes in red cell volume have been small and irregular. We have not been able to associate definite changes with parathyroid extract; neither has the blood volume borne any relation to the concentration of the blood calcium. We have noticed marked increase in the red cell volume in terminal stages of tetany, but these must be attributed to water loss through dehydration. Increases in the red cell volume during hyper-calcemia have been due to water loss through vomiting.

The effect of various types of diet upon the production of tetany in parathyroidectomized dogs is a disputed question. Patton and Findlay¹² have supported the belief that meat-feeding induces attacks of tetany. Collip and Scott² have offered evidence to the contrary, and our investigations support the findings of the later observers.

The use of parathyroid extract will undoubtedly be of greatest value clinically in tetany, a condition which certainly cannot be classified as one of the common diseases. To date, the treatment of only

one clear-cut case of tetany, with the new extract, has been reported¹⁰: a case of chronic tetany following surgical operation for thyroidectomy. Low serum calcium values of 5 mg. per 100 cc. were reported, and there was immediate benefit following the use of extract. There were the usual elevations in blood calcium after administration of the extract. The principal object of this paper is for reporting change in the blood serum calcium. We have followed calcium changes in clinical conditions in which we thought calcium metabolism might be theoretically involved. Epilepsy and paralysis agitans deserved first consideration. Three cases of paralysis agitans were studied. Berkeley and Beebe¹⁷ made a number of publications in which they reported benefit in paralysis agitans, following the use of parathyroid preparations. Their reports were rather vague. On account of the depressing effect of calcium upon nerve irritability, it was hoped that the elevation of blood calcium, by means of the extract, would serve to reduce tremor in paralysis agitans. In all of our work we have been handicapped for lack of extract, and we realize that therapeutic benefit might result from the use of larger doses. The material used in all of these experiments was sent to us for standardization, and the term units is only relative. In some of the earlier lots which we received we feel sure that the titre was considerably in excess of the theoretical amounts, as described by Collip. One of the three cases observed improved slightly, but in the other two no benefit whatever was noted. In the improved case muscle co-ordination was better, and he gained several pounds in body weight. The psychic state must, of course, be taken into consideration. In all three cases, blood calcium was elevated several milligrams, as shown in Table III.

Hemophilia is one condition which especially deserves thorough study, on account of the importance of calcium in blood coagulation. It is well known that in the absence of calcium blood will not clot. In hyper-calcemia in animals blood coagulates very quickly, and frequently it is almost impossible to obtain blood from the animals. This is due, in some measure, to the increase in the red cell volume. We have noticed decrease in coagulation time in two cases of hemophilia. In one instance it was decreased from 12½ to 5 minutes after the administration of 70 units of parathyroid extract over a period of five days. In the second case clotting was reduced

from $7\frac{1}{2}$ to 5 minutes after injecting 35 units. In the three cases of hemophilia, decidedly low calcium values were found. Hypocalcemia has been reported in certain types of hemophilia,¹⁸ with decrease in coagulation time after calcium administration. The changes in coagulation time are in all probability due to actual increase in the circulating calcium, rather than to utilization.

The blood calcium changes in several cases of mental deficiency were studied. One patient, a child of $2\frac{1}{2}$ years, received 242 units of parathyroid extract over a period of thirty-three days. Ten units of extract twice daily for four days was sufficient to elevate the serum calcium from 10.2 mg. to 15.4 mg. We continued to administer the extract in sufficient quantities to keep the serum calcium elevated to 12-14 mg. The child seemed depressed, and there was better muscle co-ordination during periods of hyper-calcemia; also, there was freedom from convulsions when the serum calcium was kept high. The slight benefit in this case was probably due to the decreased excitability incident to hyper-calcemia. In the other cases of mental deficiency no clinical changes were noted. Clinical results in epilepsy have also been negative.

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"Public Health," says the editor, Ohio State Medical Journal, "is firmly and permanently established as a principle; but we would be worse than foolish to assume that anything and everything masquerading under that banner had taken on virtue and value by merely assuming the 'name.' Commercialized fads and frauds, so-called health-by-mail agencies, self-seeking advertising clinics and 'services,' expensive and impractical socialized schemes, are all exploiting the public health idea."

REPORT OF FIFTY CASES OF DIABETES
TREATED WITH INSULIN

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In the records of these fifty patients, we found that, with few exceptions, the dietetic regime was being adhered to very religiously. There was very seldom a digestive complaint except a tendency to constipation, no doubt partially due, in some cases, to the excessive bulk found in a diabetic's diet.

DISCUSSION by Bernard Smith, Los Angeles; James W. Sherrill, La Jolla; W. D. Sansum, Santa Barbara.

THE object of this paper is to give some idea of the class of people, the symptoms, the complications, the results obtained, and the present status of the first fifty diabetics treated with insulin at the White Memorial Hospital from May 21, 1923, to July 6, 1924.

The average stay in the hospital was two weeks. Of the fifty patients under consideration, twelve were Jews. Among the diabetic patients entering more recently, there has been a still larger percentage of Jews.

The youngest patient in this list was 10 years old; the oldest, 75. The average age of the group was 52 years. Thirty were women, twenty were men. Six were standardized and sent home on a maintenance diet, without insulin. I mean by this that they were checked carefully as to tolerance for glucose by daily urine tests, careful diet restrictions, etc., and found able to handle a maintenance diet, without insulin. The rest were given insulin in order that they might have a maintenance diet. The maintenance diet given depended entirely upon age, sex, weight, and occupation of the individual. The average number of calories for men was about 2500; and for women, about 1800 calories for twenty-four hours. This is the amount of food they were finally sent home on. Each patient was given instruction on food values; was instructed how to cook; how to select foods, and how to weigh his meals. He was furnished a pair of scales that he might be accurate. Instructions were also given in regard to hypodermic injection of insulin at home, and the dangers of overdosing.

As is well known, the prominent symptoms of diabetes are loss of weight and strength, emaciation, excessive thirst, increased appetite, increased output of urine, nervousness, irritability, skin lesions (such as boils, carbuncles, itching, and eczema) and sometimes eye symptoms and neuritis.

It is of interest to compare a summary of the complaints of this group with these classical symptoms. Thirty-three complained of loss of weight and strength and of emaciation in varying degrees. Thirty-seven complained of excessive hunger and thirst in more or less severity. Eighteen complained

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